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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/804,166	02/20/97	CAMPBELL R	CAMPBELL=2A

EXAMINER

HM11/1230

BROWDY AND NEIMARK
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WASHINGTON DC 20004

ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 12/30/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on _____

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-14, 19 is/are pending in the application.
Of the above, claim(s) 7-13 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-6, 14, 19 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-14, 19 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

Part III: Detailed Office Action

Claims 1-6, 14 and 19 are pending and under consideration. Claims 7-13 remain withdrawn from prosecution as being drawn to non-elected species.

Applicants arguments filed 10/22/98 have been fully considered but are not deemed persuasive for reasons below:

Formal Matters:

The new title of the invention is acknowledged.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 14 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no basis in the specification for "a combination of antibody light and heavy chains" or "combined antibody chains" as recited in amended claim 1. Such would appear to refer to a hybrid protein comprising portions of multiple antibody chains, for which there is no basis in the specification as originally filed. This is a new matter rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 14 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 as amended is indefinite as it is not clear what is intended by "a combination of antibody light and heavy chains". Such might be intended to refer to a hybrid protein, or alternatively to multiple protein chains. Further, there is no antecedent basis for "a fragment of ..." "combined antibody chains", as there is no recitation of "combined antibody chains" elsewhere in the claim.

Claims 4 and 5 remain indefinite as it is not clear whether applicants are merely trying to indicate the orientation of the two sequences, or whether the claims are intended to limit to a direct linkage as opposed to a linkage involving a peptide linker. Applicants statement in the response that the claim is intended only to indicate orientation, and not any limitation regarding the presence of a linker has been fully considered but is not deemed persuasive. The claims must be amended accordingly. It is suggested that amendment to read "...joined, either directly, or via a linker to ...." would be remedial.

Claim 6 remains indefinite as it is not clear how the fragments "correspond" to the cited residues of TBP1. Although the claim has been amended to state "having a sequence corresponding to..." such amendment fails to address this issue.

Claim 14 remains indefinite as it is not clear how the "one or more covalent bonds" are added. Applicants traversal by reference to the specification fails to resolve the indefiniteness of the claim. Merely because a claim has support in the specification does not render the claim definite, and limitations of the specification cannot be read into the claims.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 5, 14 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al., Biol. Reprod. 52:68, reference AC cited by applicants. Johnson et al. disclose a hybrid protein comprising βhCG fused to CH_{1-3} of mouse IgG. The recombinant protein formed "multimeric forms of fusion protein" (abstract); based upon the disclosure of the composition of the protein, such would have been expected to be dimers due to disulfide bond formation between hinge regions of IgG chains. The protein was administered to rams, and thus meets the limitation of having been in the form of a pharmaceutical composition. This rejection was necessitated by the amendment of claim 1 to include in part (a) antibody chains. The ability of the hCG portion of the molecule to form heterodimers is inherent to the fusion proteins of Johnson et al. It is noted that although claim 1 requires that sequences (b) "in each of said two coexpressed sequences are *capable* of aggregating to form a dimer complex", the claim fails to specify with what they are capable of dimerizing, nor that the protein occurs as a dimer *because* of the dimerization of "sequences (b)". Thus, dimerization via the Ig constant regions as disclosed by Johnson et al. meets the limitations of the claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 14 and 19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over

Boime, U.S. Patent number 5,705,478 for reasons cited in the previous Office Action, mailed 5/22/98, at page(s) 4-5.

Applicants arguments submitted 10/19/98, paper number 9, have been fully considered but are not deemed persuasive.

Applicant argues that the conformation of the linker moiety/fused protein of Boime's fusion proteins when in a dimeric complex "would be quite different from its conformation in the "pseudodimeric" single-chain glycoprotein hormone as intended by Boime, and that the change in conformation would impair the biological function of the "linker moiety/fused protein". This argument has been fully considered but is not deemed persuasive because:

(A) While this *might* be true, it would not necessarily be true, and would be dependent upon the particular "fused protein" as well as the particular "linker moiety". Proteins are not rigid, linear strings of amino acids as would be suggested by applicant's alignments in the traversal. many "ligands" are globular proteins, which would not necessarily be adversely affected by the change in conformation between a "pseudodimer" and the dimeric conformation. For example, IL-3, IL-4, GM-CSF and M-CSF are all compact, globular proteins. Therefore, and in view of the breadth of the claims, there is no reason to expect the loss of activity urged by applicants.

(B) Applicants appear to be interpreting that the "linker moiety/fused protein" of Boime is the only portion of Boime's fusion that would meet the structural limitation of part (a) of claim 1. This is incorrect. As part (a) of claim 1 includes the generic "a ligand", and as glycoprotein hormones are most assuredly ligands, one of the glycoprotein hormone subunits of Boime's fusion protein would also meet the structural limitations of part (a) of claim 1.

(C) Applicants argue that, presumably *if* the "linker moiety/fused protein" in the pseudoheterodimer of Boime was not biologically active when the protein was in the dimeric form, that such would not meet the claim limitations. This argument has been fully considered but is not deemed persuasive because it is not established that the 'middle' protein would *not* be functional in such a dimeric configuration, because the claim does not require such activity, and because as stated in (B) above, the 'middle' portion of Boime's fusion protein is not the only portion that would meet

the requirement of being a "ligand".

Finally, applicants argue that there would be no way to "predetermine the ratio of pseudoheterodimer, dimers and higher order complexes" formed by Boime's protein. This argument has been fully considered but is not deemed persuasive because there is no such limitation to the rejected claims. Numerous of the species encompassed by the claims would similarly be capable of forming higher-order structures.

Claims 1-5, 14 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al., U.S. Patent number 5,116,964, in view of Fiddes et al., references BR and BS, cited by applicants (Nature 281:351 and 286:684).

Capon et al. teach hybrid immunoglobulin molecules, wherein a portion of an antibody is fused via recombinant DNA technology to a heterologous protein. At col. 4, line 38, they state that the molecules "serve to prolong the in vivo plasma half-life of the ligand binding partner, such as immunoglobulin domains or plasma proteins, and facilitate its purification by protein A. At column 4, beginning at line 57, they state that the molecules are "for directing ligand binding partners such as toxins, cell surface partners, enzymes, nutrient substances, growth factors, **hormones**, or effector molecules...", "...to cells bearing ligands for the ligand binding partners, and for use in facilitating purification of the ligand binding partners." (Emphasis added). At column 5, Capon et al. teach the fusion of different binding partners onto more than one chain of the immunoglobulin, to produce a multi chain polypeptide with multiple binding functions. Therapeutic and diagnostic compositions comprising the Ig fusion proteins are envisioned (column 5, line 55) . Fusion of the ligand binding partner to the Ig sequence via either the amino or carboxyl termini are envisioned, see col. 10 lines 13-15 and claim 1. Although Capon et al. disclose both the concepts of Ig fusions comprising hormones as the 'ligand binding partner' and Ig fusions comprising two or more different ligand binding partners, they do not teach or suggest specifically Ig fusions comprising one or more subunits of a heterodimeric proteinaceous hormone.

Fiddes et al. teach cDNA's encoding hCGα (reference BR) and hCGβ (reference BS). Fiddes

also teaches that "Detection of HCG by radioimmunoassay is diagnostic of pregnancy or the presence of a tumour" (reference BR, first paragraph).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the hCG sequences taught by Fiddes et al., either for hCGα or hCGβ, in the constructs of Capon et al. to produce hCG:Ig fusion proteins. One of ordinary skill in the art would have been motivated to do so to attain the known and expected advantages of such as disclosed by Capon et al., including ease of purification via protein A, and expected increased serum half life. It would further be obvious to formulate a pharmaceutical composition comprising such to, for example, be used for the production of antibodies useful in the radioimmunoassays disclosed by Fiddes et al. As was stated in the new grounds of rejection under 35 U.S.C. §102(b), above, this rejection was necessitated by the amendment of claim 1 to include in part (a) antibody chains. The ability of the hCG portion of the molecule to form heterodimers is inherent to the fusion proteins obvious over Capon et al. in view of Fiddes et al. It is noted that although claim 1 requires that sequences (b) "in each of said two coexpressed sequences are *capable* of aggregating to form a dimer complex", the claim fails to specify with what they are capable of dimerizing, nor that the protein occurs as a dimer *because* of the dimerization of "sequences (b)". Thus, dimerization via the Ig constant regions as disclosed by Capon et al. meets the limitations of the claims.

Advisory Information:

No claim is allowed. Claim 6 would be allowable if amended to overcome the above rejections under 35 U.S.C. §112.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Lila Feisee, can be reached at (703)308-2731.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should

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Advisory Information:

No claim is allowed. Claim 6 would be allowable if amended to overcome the above rejections under 35 U.S.C. §112.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

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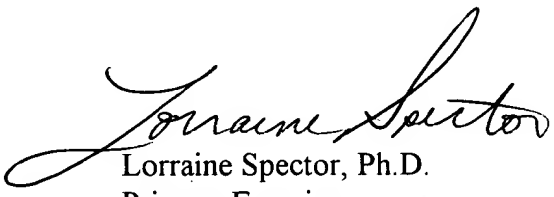
Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.



Lorraine Spector, Ph.D.
Primary Examiner

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